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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,712	11/13/2001	Nils Carlin	REF/CARLIN/509	7758

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,712	CARLIN ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *10,11,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12,13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *112700*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendments

1) Acknowledgment is made of Applicants' preliminary amendments filed 11/13/01 and 10/24/03. With these, Applicants have amended the specification.

Election

2) Acknowledgment is made of Applicants' election filed 6/23/04 in response to the written lack of unity mailed 03/24/04. Applicants have elected invention I, claims 1-9, 12, 13 and 16, with traverse. Applicants contend that claims 10 and 11 are directed to the nucleotide sequence of 5'-flanking region of a structural *thy A* gene of *Vibrio cholerae* defined by SEQ ID NO: 2 and a nucleotide sequence of 3'-flanking region of a structural *thy A* gene of *Vibrio cholerae* defined by SEQ I NO: 3 respectively, which are both comprised by the SEQ ID NO: 1 disclosed in claim 9. Applicants ask that all claims should be examined.

Applicants' arguments have been carefully considered, but are non-persuasive. As set forth below under art rejections, the first claimed nucleotide sequence, having essentially the nucleotide sequence of SEQ ID NO: 1, and a *Vibrio cholerae thy A-* strain lacking the functionality of the *thy A* gene were already disclosed in the prior art. Therefore, the special technical feature(s) does not define over the prior art. As set forth below, the method of producing a *thyA-* strain of *Vibrio cholerae* also does not define over the prior art. The lack of unity held in the instant application is proper and is hereby made FINAL.

Status of Claims

3) Claims 1-16 are pending.

Claims 10, 11, 14 and 15 are withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Elected claims 1-9, 12, 13 and 16 are under examination. A First Action on the Merits on these claims is issued.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' Information Disclosure Statement filed 11/13/01. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Sequence Listing

5) Acknowledgment is made of Applicants' submission of raw Sequence Listing and CRF filed 10/30/03.

Priority

6) The instant application is a national stage 371 application of PCT/EP99/03509, filed 05/21/1999 and claims foreign priority to the application, 9801852-6, filed 05/26/1998.

Specification

7) The specification is objected to for the following reason(s):

(a) The drawings for Figure 1 are objected to for lack of labeling of the three subparts or panels. The three panels of Figure 1 should be labeled as 1A, 1B and 1C. The figure description on page 4 of the specification should refer to the Figure as Figures 1A, 1B and 1C. Reference to these Figures throughout the specification should be amended accordingly.

(b) The use of the trademarks in the instant specification has been noted in this application. For example: 'ProMega'; 'Perkin Elmer' and 'Pharmacia'. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

Rejection(s) under 35 U.S.C § 101

8) 35 U.S.C. § 101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this cycle.

9) Claim 2 and those dependent therefrom are rejected under 35 U.S.C § 101 as being directed to a non-statutory subject matter.

Claim 2 does not sufficiently distinguish over a naturally occurring spontaneous mutant of *Vibrio cholerae* lacking the functionality of the *thyA* gene, because the claim does not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring product. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty, 447 U.S.*

303, 206 USPQ 193 (1980). The claim should be amended to indicate the hand of the inventor, e.g., by insertion of '--An isolated ..... strain ... -- if descriptive support exists for such a limitation in the instant application. See MPEP 2105.

10) Claim 9 and those dependent therefrom are rejected under 35 U.S.C § 101 as being directed to a non-statutory subject matter.

Claim 9 does not sufficiently distinguish over a naturally occurring nucleotide sequence as it exists naturally, for example, in a *Vibrio cholerae* present in the environment, because the claim does not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980)*. The claim should be amended to indicate the hand of the inventor, e.g., by insertion of --An isolated nucleotide sequence ...-- if descriptive support exists for such a limitation in the instant application. See MPEP 2105.

11) Claim 12 and those dependent therefrom are rejected under 35 U.S.C § 101 as being directed to a non-statutory subject matter.

Claim 12 does not sufficiently distinguish over a naturally occurring protein as it exists naturally, for example, in a *Vibrio cholerae*, or as it exists naturally in the environment, because the claim does not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980)*. The claim should be amended to indicate the hand of the inventor, e.g., by insertion of '--An isolated protein ...-- if descriptive support exists for such a limitation in the instant application. See MPEP 2105.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

12) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

13) Claims 1-9, 12, 13 and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 1 and 9 are indefinite and confusing in the recitation: 'gene .. having essentially the nucleotide sequence SEQ ID NO. 1', because it is unclear how much of SEQ ID NO: 1's original structure is included or excluded in the gene.

(b) Claims 3-8 lack proper antecedent basis in the limitation: 'A .... strain .... according to claim ...' as opposed to --The ..... strain ..... according to claim...--.

(c) Claim 13 lacks proper antecedent basis in the limitation: 'A protein according to claim 12'. Since claim 12 already recites a protein, for proper antecedence, it is suggested that Applicants replace the recitation with --The protein according to claim 12--.

(d) Claim 1 is confusing in the recitation '*V. cholerae* chromosome ... *thy* A gene having essentially the nucleotide sequence SEQ ID NO: 1', because it is unclear whether SEQ ID NO: 1 represents the *thy A* gene or the *V. cholerae* chromosome. If SEQ ID NO: 1 represents the *thyA* gene, it is suggested that Applicants replace the recitation with --*V. cholerae* chromosome ... *thy* A gene, said *thy* A gene having essentially the nucleotide sequence of SEQ ID NO: 1--.

(e) Claims 1, 9 and 13 are indefinite in the recitation 'of Figure ...', because the claims fail to point out what is included or excluded by the claim language. Because Figures are subject to changes via amendments even after allowance, the scope of the Figures can change which in turn would change the scope of the claims. According to M.P.E.P 2173.05(s), where possible, claims are to be complete in themselves. Incorporation by reference to Tables, Figures, or Examples as in this case, is a necessity doctrine, not for Applicants' convenience. See *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993). In the instant case, since SEQ ID numbers are recited in the claims, the recitation of 'Figure ...' appears to be unnecessary.

(f) Claim 3 is vague and confusing in the recitation 'strain .... of claim 2 ..... having a functional *thy* A gene'. Claim 3 depends from claim 2, which is drawn to a *Vibrio cholerae* strain that lacks the functionality of the *thy* A gene. Claim 3 however recites that the strain of claim 2 has a functional *thy* A gene. It is unclear whether the strain of claim 3 lacks a functional *thy* A gene or has a functional *thy* A gene.

(g) Claim 8 is vague, confusing and/or lacks proper antecedent basis in the recitation: 'the encoded protein'. Since claim 8 depends from claim 7 and includes the recitation

'heterologous protein', it is suggested that Applicants replace the recitation with --the encoded heterologous protein--.

(h) Claim 12 lacks proper antecedent basis in the recitation: 'a nucleotide sequence of a *thy* A gene ..... according to claim 9'. Since claim 12 depends from claim 9, which already recites the nucleotide sequence of the *thy* A gene of *Vibrio cholerae*, it is suggested that Applicants replace the recitation with --the nucleotide sequence of the *thy* A gene ..... according to claim 9--.

(i) Claim 16 lacks proper antecedent basis in the limitations: 'a .... *thy* A strain according to claim 2', and 'a *thy* A- strain ..... of claim 1', as opposed to --the ..... *thy* A strain according to claim 2--, and --the *thy* A- strain ..... of claim 1-- respectively.

(j) Claim 1 is indefinite and/or confusing in the limitation: 'gene nucleotides', because it is unclear what is encompassed in this limitation. The metes and bounds of the limitation and therefore the scope of the claim are indeterminate.

(k) Claims 2-8, 12, 13 and 19, which depend directly or indirectly from claim 1 or claim 9, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

14) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15) Claims 9 and 12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Valle *et al.* (*Vibrio cholerae thyA* gene. XP-002118053. EMBL Accession no. Y17135, 01 May 1998 – Applicants' IDS).

Due to the absence of a specific definition for the phrase 'essentially the nucleotide of SEQ ID NO: 1', the phrase is interpreted in this rejection as 'having a degree of sequence similarity'.

Valle *et al.* taught a *Vibrio cholerae thyA* gene comprising a nucleotide sequence that has 99.1% sequence identity with the nucleotide sequence of the instantly claimed SEQ ID NO: 1,

i.e., essentially the nucleotide sequence of the instantly claimed SEQ ID NO: 1, and a protein encoded by the same. See the four pages of XP-002118053.

Claims 9 and 12 are anticipated by Valle *et al.*

16) Claims 2 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Attridge *et al.* (*Microbial Pathogenesis* 19: 11-18, 1995 - Applicants' IDS).

Attridge *et al.* taught a vaccine comprising a *thyA* mutant of *Vibrio cholerae* (see 'Materials and Methods' and 'Results'). That such a mutant strain lacks the functionality of the *thy A* gene is inherent from the prior art teaching.

Claims 2 and 16 are anticipated by Attridge *et al.*

17) Claims 2 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mahan *et al.* (US 5,434,065).

The term 'vaccine' in claim 16 is viewed as the intended use of the product and therefore has no patentable weight.

Mahan *et al.* disclosed a *thyA* deficient non-reverting mutant *Vibrio cholerae* strain, MT173 (see Example 2), which is expected to have the inherent ability to serve as an immunizing component.

Claims 2 and 16 are anticipated by Mahan *et al.*

18) Claims 2-7 are rejected under 35 U.S.C. § 102(b) as being anticipated by Morona *et al.* (EP 0,251,579 – Applicants' IDS).

Morona *et al.* disclosed a mutant strain of *Vibrio cholerae* defective (i.e., lacking functionality) in the *thyA*+ gene. The mutant strain grows on a media containing no thymine. The mutant *thyA*- *Vibrio cholerae* strain, utilizable in a live oral vaccine, is transformed with a plasmid into which is cloned an *E. coli thyA* gene. The plasmid used for transformation of the mutant bacterial strain further comprises a gene element that expresses an antigen, such as, an outer membrane protein antigen or the O-antigen (see abstract; claims; and columns 5 and 6).

Claims 2-7 are anticipated by Morona *et al.*

Rejection(s) under 35 U.S.C. § 103

19) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in

> section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

20) Claim 8 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Morona *et al.* (EP 0,251,579 – Applicants' IDS) in view of Arntzen *et al.* (US 6,194,560).

The reference of Arntzen *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The teachings of Morona *et al.* have been explained above which do not disclose that their *thyA- Vibrio cholerae* encodes *E. coli* LTB.

However, fusion of the *E. coli* LTB to a nucleotide sequence encoding an antigen in a recombinant bacterial strain and co-expression of the antigen along with LTB was well known in the art at the time of the invention. For instance, Arntzen *et al.* taught the routine and conventional fusion of *E. coli* LTB to sequences that encode other antigens for co-expression of both, since LTB has the advantageous property of serving both as an antigen and as an adjuvant (see first full paragraph in column 14; and lines 37-41 in column 15).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention as made to fuse Arntzen's *E. coli* LTB gene into Morona's mutant *thyA- Vibrio cholerae* strain to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of advantageously enhancing immune response of the antigen(s) expressed by Morona's mutant *thyA- Vibrio cholerae* strain by expression with *E. coli* LTB which LTB is known to serve as an adjuvant in addition to serving as an antigen as taught by Arntzen *et al.*

Claim 8 is *prima facie* obvious over the prior art of record.

21) Claims 1 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Valle *et al.* (*Vibrio cholerae thyA* gene. XP-002118053. EMBL Accession no. Y17135, 01 May 1998 – Applicants' IDS) in view of Morona *et al.* (EP 0,251,579 – Applicants' IDS).

Valle *et al.* showed that *Vibrio cholerae* comprises a *thyA* gene which has a nucleotide sequence that is essentially the nucleotide sequence of the instantly recited SEQ ID NO: 1. See the four pages of XP-002118053.

Valle *et al.* do not teach a method of producing a *thyA*- strain of *V. cholerae* comprising the step of site-directed mutagenesis or deletion and/or insertion at the locus of the *thyA* gene having essentially the nucleotide sequence of the instantly recited SEQ ID NO: 1.

However, the standard technique of performing site-directed mutagenesis in the chromosome of various bacteria wherein specific genes are deleted and/or interrupted by insertion of other nucleotides was known in the art. For instance, Morona *et al.* taught inserting deletions into the chromosome of *Vibrio cholerae* by recombination between a plasmid carrying the desired deletion with adjacent flanking sequences and the *Vibrio cholerae* chromosome. Morona *et al.* taught a *thyA*- mutant of *Vibrio cholerae* strain (see abstract; and columns 5 and 6).

Given the art-known use of the standard technique of site-directed mutagenesis in *Vibrio cholerae* as taught by Morona *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to introduce a site-directed mutagenesis, i.e., deletion and/or insertion within Valle's *Vibrio cholerae thyA* gene and express it in the mutant *V. cholerae* strain in Morona's method to produce the method and the strain of the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of obtaining a method that produces a defined *thyA- Vibrio cholerae* strain for use in transformation or complementation process before using as a live oral vaccine.

Claims 1 and 16 are *prima facie* obvious over the prior art of record.

22) Claim 13 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Valle *et al.* (*Vibrio cholerae thyA* gene. XP-002118053. EMBL Accession no. Y17135, 01 May 1998 – Applicants' IDS) in view of Morona *et al.* (EP 0,251,579 – Applicants' IDS) in view of Prakash

et al. (US 6,251,866).

The reference of Prakash *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

Valle *et al.* taught the *Vibrio cholerae* protein having the amino acid sequence encoded by the *thyA* gene of *Vibrio cholerae* which is identical to the instant amino acid sequence of SEQ ID NO: 4 encoded by a nucleotide sequence that is essentially the same nucleotide sequence as the instant SEQ ID NO: 1. The protein recited in the instant claim is the same as the protein disclosed by Valle *et al.* except for the first two amino acids, Val Lys, in place of Met Arg in the instantly recited SEQ ID NO: 4. See the amino acid sequence of Valle *et al.*

However, Valle's amino acid residues, valine and lysine, are amino acids that are considered in the art as 'biologically functionally equivalent' conservative amino acids (see third full paragraph in column 5 of Prakash *et al.*), replacement with which is routinely practiced in the art. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention as made to replace the first two amino acids, valine and lysine, in Valle's protein with the art-known functionally equivalent or conservative amino acids, methionine and arginine respectively, to produce the protein of the instant invention, with a reasonable expectation of success. The conservative substitution with methionine and arginine in place of valine and lysine respectively of Valle's protein is well within the realm of routine experimentation, would have been obvious to one of ordinary skill in the art, and would have resulted in a protein which has substantially the same function(s) as Valle's protein given that methionine and arginine are taught in the art to be 'functionally equivalent'.

Claim 13 is *prima facie* obvious over the prior art of record.

Remarks

23) Claims 1-9, 12, 13 and 16 stand rejected.

24) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (703) 872-

9306.

25) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

26) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

September, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER